

Pharmacology

A-Drugs acting by enzyme inhibition:

1- α -methyldopa : inhibits dopa-decarboxylase enzyme

(Used in treatment of hypertension, it is the drug of choice in hypertension during pregnancy).

2-Anti-cholinesterase: either reversible as physostigmine and neostigmine, or irreversible as organophosphorous compounds.

3-Glucocorticoids (cortisone): inhibits phospholipase A_2 .

4-NSAIDs e.g. Aspirin, phenylbutazone, Diclofenac....., inhibit cyclooxygenase enzymes (COX).

5-Zileuton: inhibits 5-lipoxygenase enzyme $\rightarrow$ $\downarrow$ leukotriene synthesis, used in prophylaxis of bronchial asthma.

6-Dazoxiben: Antiplatelet by inhibition of thromboxane A_2 synthase (same mechanism as aspirin as antiplatelet).

7-Methylxanthines e.g. theophylline and aminophylline, inhibit P.D.E (phosphodiesterase) type IV (4) $\rightarrow$ $\uparrow$ c-AMP $\rightarrow$ CNS stimulation, cardiac stimulation, V.D. and bronchodilation.

8-Disodium cromoglycate and Nedocromil sodium: (mast cell stabilizers)

Used in prophylaxis of bronchial asthma, given by inhalation, inhibit P.D.E in mast cell.

9-Warfarin: "oral anticoagulant", inhibits vitamin K reductase $\rightarrow$

$\downarrow$ Synthesis of prothrombin II (2) and other coagulation factors (VII, IX, X).

10-Dipyridamole: Antiplatelet, $\downarrow$ PDE $\rightarrow$ $\uparrow$ c-AMP.

11-pentoxifylline: methylxanthine, antiplatelet, as dipyridamole.

12-Statins: antihyperlipidaemics, $\downarrow$ HMG.CO.A reductase enzyme.

13-Carbonic anhydrase inhibitors: e.g. acetazolamide (diamox) used as diuretic (self-limiting), $\downarrow$ IOP in glaucoma, treatment of petit-mal epilepsy, as alkalinizer of urine.

14-Angiotensin converting enzyme (ACE) inhibitors: e.g. captopril, lisinopril, enalapril, used in treatment of hypertension (drugs of choice in hypertension + diabetes mellitus), and in congestive heart failure.

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15-Digitalis (cardiac glycosides): inhibit Na^+/K^+ ATPase (Na^+ pump), used in treatment of heart failure.

16-Bipyridines: e.g. amrinone, milrinone, eroximone, inhibit P.D.E type iii (3) , used in resistant heart failure as short term therapy.

17-Proton pump inhibitors: e.g. dmeprazole, lansoprazole. Inhibit H^+/K^+ ATPase (proton pump) in parietal cells, used as antisecretory ($\downarrow \text{HCl}$) in treatment of peptic ulcer.

18-Allopurinol: xanthine oxidase inhibitors, $\downarrow$ uric acid synthesis in prophylaxis of gout.

19- MAO Inhibitors.

20-peripheral dopa-decarboxylase inhibitors (PDDI) e.g. carbidopa and beuserazide, combined with L-dopa in treatment of Parkinsonism.

21- COMT-Inhibitors: tolcapone and entacapone, given with L-dopa/carbidopa in treatment of Parkinsonism.

22-Sodium valproate and vigabartin: Inhibit GABA transaminase, used in epilepsy (broad-spectrum anti epileptics).

23- β -lactamase inhibitors: e.g. clavulanic acid, sulbactam and tazobactam, combined with penicillin to treat β -lactamase producing bacteria e.g. staph.

24-Cilastatin: inhibits dipeptidase enzyme in renal cells to inhibit metabolism of imipenem into nephrotic metabolite (imipenem + cilastatin = tienam).

25-sulphonamides: inhibit dihydropteroate enzyme $\rightarrow \downarrow$ synthesis of dihydrofolic acid from PAPA by bacteria.

26- Trimethoprim

27-pyrimethamine

28-proguanil:

29-Methotrexate: anticancer, inhibits dihydrofolate reductase, causes megaloblastic anemia, treated by folinic acid (=leukovorin).

30-Rifampicin: inhibits DNA-dependent RNA polymerase.

31-Quinolones and fluoroquinolones: inhibits DNA-gyrase.

32-Acyclovir: Antiviral inhibits DNA polymerase.

33-Zidovudine: Antiviral, used in treatment of AIDS, inhibits reverse transcriptase enzyme.

B-Drugs that inhibit phosphodiesterase enzymes (P.D.E Inhibitors)

:

- 1 Selective α_1 -blockers (e.g. prazosin , they do not cause reflex

- tachycardia as they increase cAMP & cGMP)
- 2 Bipyridines (*Amrinone* , *Milrinone* , *Enoximone*) :Inhibit PDE III ⁽³⁾
 - 3 Methyl Xanthines (*Aminophylline* , *caffeine* , *theophylline* , *theobromine*): Inhibit PDE IV ⁽⁴⁾
 - 4 *Sildenafil* (Viagra) , *Tadalafil* , *Valdenafil* used in erectile dysfunction : Inhibit PDE V ⁽⁵⁾
 - 5 *Dipyridamole* : anti platelet

Drugs & git:

A-Drugs causing Hepatotoxicity:

1. α -methyl dopa(α 2-agonist-antiadrenergic-used in treatment of hypertension, is the drug of choice in hypertension during pregnancy).
2. Dantrole (direct skeletal muscle relaxant, ↓Ca release from sarcoplasmic reticulum, life-saving in malignant hyperthermia and neuroleptic malignant syndrome , given I.V).
3. Statins e.g; simvastatin (anti-hyperlipidemics).
4. Fibrates e.g; clofibrate (anti-hyperlipidemic).
5. Toxic doses of paracetamol (or if given with HME inhibitors as alcohol and phenobarbitone) due to accumulation of NABQI.
6. Colchicine (anti-inflammatory in gout).
7. Tolcapone(COMT-inhibitor used in parkinsonism with L-dopa).
8. Phenytoin(anti-epileptic+anti-arrhythmic).
9. Oxazolidinediones(anti-epileptic in petit-mal epilepsy).
10. Sodium Valproate (broad-spectrum antiepileptic).
11. MAO-inhibitors (anti-depressants).
12. Halothane (inhaled general anaesthetic).
13. Tetracyclines(antibiotics).
14. Sulphonamides(anti-bacterial).
15. Isoniazid.
16. Pyrazinamide.
17. Ethionamide.

18. Para-amino-salicylic acid.

19. Ketoconazole.

20. Griseofulvin.

21. Cis-platin (anti-cancer).

B-Drugs causing Diarrhea:

1-Parasympathomimetics: e.g Carbachol - Bethanecol -Neostigmine
(Stimulate M Receptors in Small Intestine)

2-Adrenergic Neurone Depressants : e.g Guanethidine -Reserpine
(They causes Parasympathetic Predominance)

3-Dantrolene which is direct skeletal muscle Relaxant

4- Oral Iron : e.g Ferrous Fermanate & Gluconate ,May cause black or bloody diarrhea

(Some oral iron causes constipation)

5-Magansium Oxide -Hydroxide -Trisilicate :used as Chemical antacids

6-Metoclopramide : Antemetic & Prokinetic

7-Domperidone: Antiemetic & Prokinetic

8-Purgatives (chemical & physical)

9-Colchicine : used in Acute gouty arthritis, may causes bloody diarrhea

10- Erthromycin : Anthmicrobial (Diarrhea is due to prokinetic

11-Broad Spectrum Antimicrobials (especially if not completely absorbed)

e.g Ampicillin -Tetracyclines- Chloramphenicol -Cephalosporins

(Due to Superinfection)

12-PG-Analogues :e.g Misoprostol (see Peptic ulcer)

C-Drugs Causing Constipation:

1-Antimuscarinic Drugs (Anticholinergic Drug =Parasympatholytics)

e.g: Atropine -Hyoscine-Antisecretory -Antispasmodic -Atropine substitutes

2-Opioid Analgesics: e.g Morphine -Meperidine -Loperamide-diphenoxylate (note that loperamide and diphenoxylate are not analgesics) they stimulate opioid receptors in GIT

3-Aluminum Hydroxide Gel :Act as Chemical & physical Antacid

- 4-Calcium Carbonate :chemical Antacid
- 5-Calcium channel blockers :e.g Nifedipine -Verapamil
- 6-Drugs Having marked " Atropine-like Action";e.g
 - 1st Generation (=sedating) Anti-histaminics as Diphenhydramine
 - Disopyramide : class I-Anti-arrhythmic
 - Tricyclic anti-depressants as imipramin
 - Carbamazepine : Anti-epileptic

D-Drugs Causing Nausea & Vomiting:

- 1-Opioid Analgesics :e.g Morphine ,Methadone ,Meperidine
- 2-Cardiac Glycosides (Digitalis) :e.g Digoxin ,digitoxin
- 3-Methylxanthin :e.g Aminophylline , Theophylline
- 4-D2-Agonists :e.g L-Dopa , Bromocriptine
- 5-Estrogen (oral contraceptive) causes mainly nausea
- 6-Cancer chemotherapy

E-Drugs causing Allergic Cholestatic Hepatitis :

- 1. Carbamazepine(anti-epileptic).
- 2. Tricyclic antidepressants (TCA's).
- 3. Chlorpromazine (anti-psychotic).
- 4. Erythromycin (antibiotic).
- 5. Chlorpromazine (anti-diabetic).
- 6. Oral contraceptives.
- 7. Rifampicin(anti-T.B)
- 8. H₂-blockers as Cimetidine (anti-ulcer).

F-Drugs activated by gastric acidic medium:

- 1-Chlorazepate (Benzodiazepine: anxiolytic &hypnotic)
- 2-Proton Pump Inhibitors e.g. Omeprazole (Antisecretory drugs used in treatment of peptic ulcer)
- 3-Sucralfate (mucosal protective agent, used to prevent recurrence)

N.B.:

Ketoconazole (Antifungal) absorption increases in acidic medium

G-Drugs destroyed by gastric acid:

1-Acid-sensitive penicillins(e.g. benzyl penicillin, procaine penicillin , benzathine penicillin , methicillin , cabencillin , ureido-penicillins)

2- Erythromycin (to protect against HCL, erythromycin is given as enteric-coated tablets, or estolate ester is added to erythromycin)

H-Drugs destroyed by proteolytic enzymes: (Not effective orally)

1- Polypeptide antibiotics: Bacitracin & Polymixins

2- Polypeptide hormones: e.g. Insulin, Growth hormone, Glucagon, ACTH, ADH (vasopressin)

3-Drugs and cardiovascular system:

A-Drugs Causing Bradycardia:

1- β -blocker: e.g Propranolol ,Nadolol , Atenololetc

2-Parasympathomimetics (Muscarinic Agonists):e.g Methocholidine ,Carbachol ,...

3-Digitalis (The Earliest manifestation of toxicity are nausea & vomiting +Bradycardia below 60 beats /min)

4- α_1 -Agonists causes reflex Bradycardia (α_1 stimulation $\rightarrow$ V.C $\rightarrow$ increase B.P $\rightarrow$ reflex bradycardia through baro receptors action)

5-General Anaesthesia :e.g Halothane due to increase vagal tone

6-Some calcium channel blockers :e.g Verapamil (due to Blocking Voltage-gated Ca channels in heart)

B-Drugs causing Postural Hypotension (Orthostatic Hypotension OR Syncope) :

1. Nitrates as *Nitroglycerine* (used in treatment of Angina pectoris)
2. α_1 -blockers (*phentolamine* , *phenoxybenzamine* , BUT selective α_1 -blockers as *prazosine* cause "1st dose phenomenon")
3. Ganglion blockers (they cause *Atropine* like side effect + postural hypotension + sexual dysfunction in males)
4. Adrenergic neurone blockers: (*Guanithidine* , *reserpine* , α -methyl dopa which causes minimal hypotension)

C-Drugs used in treatment of Postural Hypotension :

1. *Noradrenaline* (IV infusion) Catecholamine
2. *Ephedrine* (oral & IV)
3. *Phenylephrine* (oral & IV) Non-catecholamine
4. *Methoxamine* (oral & IV)
5. *Midodrine* (oral)

N.B. : - All previous drugs are α_1 -agonists

- They are given by I.V. injection in case of "Acute" postural hypotension due to spinal anesthesia
- They are given orally (except *noradrenaline*) in case of "chronic" postural hypotension

D-Drugs used in treatment of PVD :

1. α_1 -blockers (except *ergotamine* , *ergotoxine* , *dihydroergotamine* , *yohimbine*)
2. β_2 -Agonists (e.g. *Nylidrin* , *isoxsuprine*)
3. M_3 -Agonists = parasympathomimetics (e.g. *Methacholine*)
4. Calcium channel blockers e.g. *Nifedipine*
5. PGI_2 : *Epoprostenol*
6. *Dihydroergotoxine* (the only ergot alkaloid useful in PVD)

E-Drugs contraindicated in PVD :

1. α_1 -Agonists
2. Ergot alkaloids (except dihydroergotoxine)
3. Non selective β -blockers

F-Drugs used in treatment of paroxysmal atrial tachycardia (PAT) :

1. β -blockers
2. M_2 -Agonists (e.g. Methacholine, Edrophonium, Neostigmine)
3. Digitalis (cardiac glycosides)
4. Anti Arrhythmic drugs : quinidine, Ca^{2+} -channel blockers (e.g. verapamil)
5. α_1 -Agonists: e.g. Noradrenaline, phenylephrine, Methoxamine (causes reflex bradycardia following elevation of blood pressure & contraindicated in hypertensive patients)

G-Drugs contraindicated in PAT :

1. β_1 -Agonists: e.g. Adrenaline, isoprenaline, ephedrine
2. M_2 -antagonists: e.g. Atropine, Gallamine
3. α_1 -antagonists: due to hypotension followed by reflex tachycardia (except selective α_1 -blockers as prazosin)
4. Arteriodilators (e.g. Hydralazine, Minoxidil, β_2 -agonists due to reflex tachycardia following hypotension)

(Atropine is non-selective muscarinic antagonist whereas Gallamine is a competitive neuromuscular blocker that block Nm receptors and also blocks cardiac M_2 -receptors)

H-Drugs causing Tachycardia:

- 1- β_1 -agonists : e.g. Adrenaline, Isoprenaline, Ephedrine
- 2- β_2 -agonist : e.g. Salbutamol, Ritodrine

β_2 -stimulation lead to :V.D :decrease B.P :reflex tachycardia & may be due to β_1 stimulation by large doses because Selectivity is not absolute

- 3-Atropine(antimuscarinic =parasympatholitic) , note that atropine may Cause initial bradycardia due to block of presynaptic M-receptors that cause increasing release of acetylcholine or due to stimulation of C.I.C
- 4-Methylxanthines : e.g. Aminophylline , theophylline , by inhibition of P.D.E type 4 & increase C-AMP
- 5-Arteriodilators : e.g. nifedipine (and other dihydropyridine Ca²⁺ Chanel blockers) , hydralazine , minoxidil , (nitrates are mainly Venodilatores but may cause arteriodilatation) . Arteriodilators Cause reflex tachycardia
- 6-Glucagon hormone (increase C-AMP by stimulation of adenylcyclase)
- 7-Alpha 1-blockers : e.g. phentolamine , phenoxybentamine , they cause reflex tachycardia due to arteriodilatation , note that selective alpha1-blockers as prazosin cause no (or minimal) tachycardia.
- 8-Ganglion blockers : e.g. Trimethaphan

I-Drugs causong hypokalemia :

- 1- Thiazide diuretics
- 2- Loop diuretics
- 3- C.A. Inhibitors
- 4- Steroids (Aldosterone - cortisone)
- 5- Adrenaline (and other drugs acting as β_2 -Agonists) due to uptake of K⁺ from blood into skeletal muscles.

J-Drugs causing hyperkalemia :

- 1 K⁺-sparing diuretics
 - 2 ACE-Inhibitors (*Captopril* ,)
 - 3 ARBs (*Losartan* ,)
 - 4 Drugs that inhibit Aldosterone synthesis (e.g. *Metyropone* , see hormones)
 - 5 *Succinycholine*
 - 6 Non-seletive β -Blocker (e.g. *propranolol*)
- N.B. *Digitalis* does not cause hypokalemia , but hypokalemia induces *digitalis* toxicity.

K-Drugs that are contraindicated in porphyria

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- 1-Barbiturates (phenobarbitones , thiopentone ...)
- 2-Primidone (antiepileptic , partially metabolized into phenobarbitone)
- 3- Eriseofulvin (antifungal used for treatment of muco-cutaneous fungal infection
- 4-Chloroquine (anti-malarial + anti -ameobic + anti-giardiasis
+anti-inflammatory in R.A .)

4-Drugs and nervous system:

A-Therapeutic uses of sympathomimetics :

1. Shock : *Adrenaline* is life-saving in anaphylactic shock ,
Dopamine in hypovolemic & cardiogenic shock ,
Dobutamine in cardiogenic shock
(in Hypovolemic shock fill up then open up)
2. Acute attacks of bronchial asthma :
Adrenaline , *isoprenaline* (non selective) *salbutamol* , *terbutaline* , *fenoterol* ,
reproterol
(short acting selective B₂ agonists)
3. Prophylaxis of Bronchial asthma :
Ephedrine (non selective & CNS stimulant) ,
Hexoprenaline & *Isoetharine* (catecholamines)-selective B₂-agonists ,
Salmetrol & *formoterol* (long acting selective B₂-agonists)
4. Peripheral Vascular Diseases (PVD) e.g. Raynaud's diseases
Nylidrin , *Isoxsuprine*
5. Uterine relaxants (tocolytics) in contraction ring of the uterus , premature labor , threatened abortion , dysmenorrhea :
Ritodrine , *salbutamol* , *isoxsuprine* : Selective B₂-agonists
Adrenaline : Non-selective
6. Vasopressors in treatment of hypotension (see above)
7. Nasal decongestants : *Naphazoline* , *tetrahydrozoline* , *xylometazoline* ,
phenyl propanolamine , *ephedrine* (causes rebound congestion) ,
pseudoephedrine , *phenylephrine* , *methoxamine*

8. AV block (Heart block) : *Isoprenaline (S.L.) , Dobutamine (I.V. infusion)*
9. Nocturnal Enuresis : *Ephedrine*
10. Narcolepsy (Hypersomnia) : *Amphetamine*
11. Attention Deficit Hyperkinetic Disorder (ADHD) :
Methylphenidate , Amphetamine
12. Anorexigenic drugs in obesity : *phenmetrazine , diphenmetrazine , diethypropion , amphetamine (not used)*
13. Acute heart failure :
Dopamine , Dobutamine , Dopexamine : I.V. infusion
14. Chronic heart failure : *Prenaterol (oral)*
15. Glaucoma (open-angle) :
Adrenaline , Dipivefrin (prodrug , better than adrenaline)
16. Cardiac resuscitation in cardiac arrest : *Adrenaline (intra cardiac)*
17. Mydriatics for fundus examination : (α_1 -agonists as *Ephedrine-Phenylephrine*)
18. Paroxysmal atrial tachycardia : (α_1 -agonists as *phenylephrine*)
19. Hemostatics in cases of bleeding as Epistaxis but not in hypertensive patients (*adrenaline-ephedrine-phenylephrine-methoxamine*)
20. To prolong duration of local anesthetics but not in fingers , toes & circumcision : *Adrenaline , Ephedrine , phenylephrine , methoxamine*
21. Acute hypoglycemia due to overdose of insulin or oral hypoglycemic drugs:
Adrenaline (I.V. glucose is better)

B-Drugs causing Convulsions (Seizures):

- 1-CNS stimulants: a-Methylxanthines (Theophylline)
 - b-Amphetamine
 - c-Cocaine
 - d- Atropine
 - e-Aralectics (brain stem stimulants)
 - f- Strychnine (spinal cord stimulant)
- 2- Morphine (by decrease release of GABA)
- 3-Meperidine (metabolized into normeperidine +atropine like action)
- 4-Aspirin (acute toxicity) due to increase Glutamate /GABA ratio
- 5-Chlorpromazine (major tranquilizer = Antipsychotic = Neuroleptic)
- 6-MAO-inhibitors
- 7-Lithium (anti-manic, mood stabilizer in bipolar disorders)
- 8-Penicillins (if large dose or intrathecal injection)
- 9-Carapenem e.g. Imipenem (B-lactam antibiotics)

- 10-Cycloserine (antibacterial _ inhibits cell wall synthesis)
- 11-Fluoroquinolones especially with NSAIDS & theophyllin
- 12-Amphotericin B (polyene -antifungal)
- 13-Oxamniquine (Anti bilharzial)
- 14-Cardiac glycosides

C-Drugs causing psychosis:

- 1-D2-Agonist e.g. L-dopa , bromocriptine (antiparkinsonian drugs)
- 2-Indomethacin (NSAID)
- 3-Glucocorticoids
- 4-Cycloserine
- 5-Cardiac glycosides

D-Drugs causing Depression:

- 1- Estrogen (oral contraceptives)
- 2-Reserpine (adrenergic neurone depressant, depletes the brain from monoamines :5HT , noradrenaline & dopamine)
- 3- Alpha -methyldopa (decrease synthesis of monoamines by decrease dopa decarboxylase)
- 4-Chlorpromazine (causes pseudo-depression)

5- Drugs and the urinary system:

A-Drugs causing Nephrotoxicity

:

- 1-**NSAIDs** except paracetamol (cause "analgesic nephropathy" due to renal V.C. by ↓ PGE and PGI synthesis).
- 2-**Colchicine** (+ hematuria).
- 3-**Gold salts** (in treatment of rheumatoid arthritis).

4-Vancomycin.

Anti-Bacterial

5-Aminoglycosides.

6-Cephalosporins.

7-Methicillin.

8-Sulphonamides.

9-Tetracyclines(especially of expired = Fanconi syndrome).

10-Amphotericin B (Anti-fungal).

11-Acyclovir(Anti-viral).

12-Demeclocycline(Anti-bacterial tetracycline).

13-Lithium(Anti-manic + mood stabilizer).

14-Methoxyflurane(inhalant general anaesthesia as halothane).

B-Diuretics causing Hypokalemia:

- 1 Thiazide diuretics (e.g. hydrochlorothiazide)
- 2 Loop diuretics (e.g. furosemide, ethacrynic acid)
- 3 Carbonic anhydrase inhibitors (e.g. Acetazolamide, methazolamide)

C-Diuretics causing hyperkalemia = K⁺ sparing diuretics

- 1 Spironolactone

Aldosterone antagonists

- 2 Canrenone

- 3-Trimetaphane

Non-Aldosterone antagonists

- 4-Amiloride

D-Diuretics causing alkalosis :

- 1 Thiazide diuretics
- 2 Loop diuretics

E-Diuretics causing acidosis :

- 1 K^+ sparing diuretics
- 2 Carbonic anhydrase inhibitors
- 3 Acidifying diuretics (NH_4Cl)

Cause hyperchromic acidosis

F-Self - limiting diuretics :

They cause acidosis leading to reabsorption of Na^+ in exchange for H^+ or NH_4^+

- 1 Carbonic anhydrase inhibitors
- 2 Acidifying diuretics

G-Diuretics causing hypercalcemia :

- 1 Thiazide diuretics
- 2 Non-aldosterone antagonists

H-Diuretics causing hypocalcemia :

- 1 Loop diuretics
- 2 *Spironolactone* (Aldosterone antagonist)

6-Teratogenic drugs:

- 1-**NSAIDs** except paracetamol(Aspirin causes cardiac septal defect,but is the safest NSAID).
- 2-**Benzodiazepines.**
- 3-**Barbiturates.**
- 4-**Chlorpromazine**(phenothiazine antipsychotic and anti emetic).
- 5-**Lithium.**
- 6-**ACE-inhibitors** e.g. Captopril.
- 7- **AT₁_(Angiotensin) receptor-antagonists** e.g. Losartan.
- 8-**Antihistaminics** e.g. Cyclizine and Meclizine.
- 9-**Oral anticoagulants** e.g. Warfarin.
- 10-**Thiazide and Loop diuretics.**

11-Phenytoin. :

12-carbamazepine.

13- **Sodium valproate**: antiepileptic, causes spina bifida.

14-**Nitrous oxide**(inhaled gas general anesthetic).

15-**Sodium nitropruside**(mixed vasodilators given I.V. infusion)

16-**Aminoglycosides**→fetal deafness.

17-**Tetracyclines**.

18-**Sulphonamides**→hyperbilirubinemia and kernicterus.

19-**Quinolones**→damage of growing cartilage and arrest of growth.

20-**Griseofulvin**(antifungal).

N.B. 1-**Morphine** is not teratogenic but cause "fetal Addiction".

2-**Thalidomide** was used as anxiolytic / hypnotic and it caused "Amelia"= absent limbs and "phocomelia"= short limbs (thalidomide catastrophe)

7-Prodrugs --→ Active drugs---→Active metabolite:

Prodrugs:

- 1 Inactive drugs converted in the body into active metabolites.
- 2 Activation usually occurs in the liver.
- 3 Chlorazepate is converted into active metabolite nordiazepam in the stomach by gastric acid.

EXAMPLES:

1. Dipivefrin (used in glaucoma).
2. Phenoxybenzamine (α -blocker).
3. Hexoprenaline (selective β_2 agonist used in bronchial asthma, it is a non-catecholamine, converted to active metabolite by COMT).
4. Minoxidil (antihypertensive, converted into minoxidil sulphate).
5. Enalapril, Fosinopril, Ramipril (ACE inhibitors).
6. Proton pump inhibitors, e.g; Omeprazole (in treatment of peptic ulcer).
7. Cortisone is converted into cortisol (=hydrocortisone).
8. Sulindac and Nabumetone (NSAID).
9. Ampicillin esters(=pro-ampicillins) as Bacampicillin, Pivampicillin, Talampicillin, converted into ampicillin in

- liver and GIT mucosa.
10. Chlorazepate (Benzodiazepine).
 11. Propacetamol→Paracetamol, given by injection.

Active drugs converted into active metabolites:

1. Phenacetin→ Paracetamol= Acetaminophen (analgesic-antipyretic).
2. Benzodiazepines except LOT-Nitrazepam-Clonazepam.
3. Morphine→Morphine-6-glucuronide.
4. TCA's e.g; Imipramine→Desipramine, Amitriptyline→Nortriptyline.
5. Spironolactone→Canrenone (Aldosterone-antagonist K-sparing diuretic).

8-Iatrogenic diseases: Examples of **Iatrogenic (Drug-induced) Diseases :**

Drugs	Disease
- NSAIDS (except paraacetamol) - Glucocorticoids	1- peptic ulcer
- NSAIDS (except paraacetamol) - Morphine - Non-selective B-blockers (propranolol) - Muscarinic agonists, e.g: Methacholine, Carbachol, Neostigmine	2- Bronchial Asthma
- Glucocorticoids - oral contraceptives - Alpha1-agonists (adrenaline-noradrenaline, phenylephrine-ephedrine, phenylpropranolamine)	3- Hypertension
- B1-agonist (adrenaline-isoprenaline) - Thyroid hormones - Methyl xanthines - Arteriodilators (hydralazine, minoxidil, nifedipine....) due to reflex tachycardia	4- Angina pectoris

- Atropine - Hyoscine - Atropine substitutes - Atropine- like drugs - ganglion blockers - vasodilators (e.g:nitrates) - Glucocorticoids	5- Glaucoma
- Hydralazine (arteriodilator used as anti hypertensive) - Procainamide (class I.A anti arrhythmic) - Isoniazid (anti T.B) (They cause iatrogenic SLE especially in slow acetylators)	6- Systemic Lupus Erythematosus (SLE)
- D2-blockers (e.g:phenothiazines as Chlorpromazine, butyrophenones as haloperidol, metoclopramide) - Reserpine - Alpha-methyl dopa	7- Parkinsonism
- Glucocorticoides (given systemically for long duration)	8- Cushing Syndrome
- Digitalis - verapamil - B-blockers - Methacholine	9- AV block (Heart block)
- Salicylates (tinnitus I the most important manifestation of salicylism) - Ototoxic drugs, e.g: loop diuretics, aminoglycosides, vancomycin - Metronidazole - Minocycline - Indomethacin and phenylbutazone	10- Tinnitus Vertigo

9-Drugs used for diagnostic tests:

Drug	Diagnosis of
1-Phentolamine (non-selective α -blocker)	Sustained type of pheochromocytoma (Phentolamine cause <u>severe</u> hypotension in these patients). "Regtive test"
2-Clonidine (central α_2 -agonist)	Sustained type of pheochromocytoma = clonidine suppression test (Clonidine <u>can't</u> supress release of catecholamines from the

	tumor)
3- <i>Methacholine</i> (M-agonist) 4- <i>Histamine</i> (Autacoid)	Paroxysmal type of pheochromocytoma = provocative test (they cause hypertension in patients with pheochromocytoma instead of hypotension in other patients)
5- <i>Ergotamine</i> (ergot alkaloid-oxytocic-weak α_1 -agonist)	Prinzmetal (variant or vasospastic) angina. (<i>Ergotamine</i> causes marked coronary V.C. in these patients)
6- <i>Adrenaline</i> (sympathomimetic-catecholamine- β and α agonist)	Acute hemorrhagic pancreatitis (Lewi's test). (<i>Adrenaline</i> causes active mydriasis in this case)
7- <i>Methacholine</i> (M-agonist)	Bronchial asthma = provocative test (<i>Methacholine</i> causes marked bronchospasm and inc. bronchial secretion in these patients)
8- <i>Edrophonium</i> I.V. 9- <i>Neostigmine</i> I.M. + <i>Atropine</i> (<i>Edrophonium</i> and <i>neostigmine</i> are reversible anti-cholinesterases)	Myasthenia gravis
10- <i>Edrophonium</i> I.V.	Differentiation between myasthenic and cholinergic crisis in patients of myasthenia gravis.
11- <i>Ampicillin</i>	Infections mononucleosis (<i>Ampicillin</i> causes maculopopular rash). "See chemotherapy"

10-Acute toxicity of the drues:

Signs and symptoms of acute toxicity (overdose)	Drugs causing toxicity
Hallucinations (shizophrenia-like) – convulsions – hypertension – active mydriasis – coma and finally inhibition of R.C.	1- <i>Amphetamine</i> 2- <i>Cocaine</i>

Mania - hallucinations - convulsions - hypertension followed by hypotension - hyperpyrexia - bradycardia - nausea & vomiting - coma and finally inhibition of R.C.	<i>Ergot alkaloids</i> (Ergotism) due to overdose of ergotamine or eating rye grains infected by ergot fungus.
Bradycardia - hypotension - bronchospasm and increased bronchial secretion - excessive secretion - diarrhea - urination - miosis - skeletal muscle twitches followed by paralysis - convulsions - followed by coma and inhibition of R.C.	<i>Organophosphorus compound</i> poisoning.
Mania - hallucinations - convulsions - hypotension - tachycardia - passive mydriasis - dry hot skin (flush & fever) - constipation - urine retention - finally coma and inhibition of R.C.	<i>Atropine</i>
Apnea (due to paralysis of respiratory muscles) - hypotension - tachycardia - bronchospasm	Competitive neuro - muscular blockers as <i>curare</i>
Coma + inhibition of R.C. + pin point pupil	<i>Morphine</i> (see CNS)

- 1 The cause of death in acute toxicity is due to depression of R.C., i.e central respiratory failure.
- 2 Competitive neuro-muscular blockers cause peripheral respiratory failure but not central because they don't cross B.B.B
- 3 Organophosphorus compound poisoning cause both central and peripheral respiratory failure.
- 4 General rules for treatment of acute drug toxicity :
 1. Stomach wash = gastric lavage (if the drug is ingested**)
 2. Care for respiration (endotracheal intubation - artificial respiration)
 3. Antidote (if there is a specific antidote , e.g. atropine for organophosphorus poisoning , neostigmine for curare toxicity , physostigmine for atropine poisoning)
 4. Symptomatic treatment (e.g. anticonvulsant as diazepam)
 5. Increase (promote) renal excretion of the drug (by changing pH of urine : Acidification of urine in toxicity of basic drugs as amphetamine and ephedrine using ammonium chloride or ascorbic acid , Alkalinization of urine in toxicity of acidic drugs as *salicylates* (aspirin) using NaHCO_3 . The drug should be completely or partially excreted in urine unchanged)

** In acute *morphine* toxicity stomach wash is performed although *morphine* is given by I.V. injection!! (see CNS)

N.B : The size of the pupil is a useful diagnostic sign.

* Therapeutic uses of choline esters:

Choline esters include:	Therapeutic uses:
1- <i>Acetylcholine</i> (natural)	None (must be given I.V. - very short duration - non-selective M-agonist)
2- <i>Methacholine</i>	1.Provocative test in diagnosis of bronchial asthma 2.P.V.D. 3.P.A.T 4.Provocative test in diagnosis of paroxysmal type of pheochromocytoma
3- <i>Carbachol</i> 4- <i>Bethanechol</i>	1.Glucoma (eye drops) 2.Non-obstructive post-operative paralytic ileus 3.Non-obstructive post-operative (or post-partum) urine retention
5- <i>Succinylcholine</i> (Depolarizing neuro - muscular blocker)	1.Adjuvant to general anaesthesia 2.Endotracheal intubation

N.B. : - All except *Acetylcholine* are synthetic.

- All are quaternary ammonium compounds.

- All except *succinylcholine* are parasympathomimetic.

11-Causes & Examples of Cross allergy :

1-Similarity in the chemical structure of different drugs e.g.

_Penicillins & Cephalosporins

_Sulphonamides & thiazide diuretics, loop diuretics, Carbonic anhydrase inhibitors ,& Sulphonylureas.

2- Similarity in the mechanism of action e.g.

_ Aspirin & other NSAIDS (except paracetamol):Bronchial asthma

12-Drugs that should never be stopped SUDDENLY (abruptly)

1. β -blockers : sudden withdrawal causes rebound tachycardia , arrhythmia , angina & even acute myocardial infarction
2. *Clonidine* (and other selective α_2 -agonists) : sudden withdrawal causes "rebound hypertension" which is treated by giving *clonidine* again or by α_1 -blocker $\pm$ β -blocker or *labetolol* but never use non-selective β -blocker alone
3. *Noradrenaline* IV infusion : sudden withdrawal cause "rebound hypotension"
4. Corticosteroids : sudden withdrawal after chronic use causes "Acute Addisonian crisis"

13-Drugs and pheochromocytoma

Drugs used in treatment of pheochromocytoma (If inoperable):

1. α_1 -Blockers , especially *phenoxybenzamine* because it is a non-competitive irreversible blocker and is the most potent α -Blocker.
2. Labetalol ($\beta_1 + \alpha_1$ Blocker).
3. β -Blockers may be added to α -Blocker but never use non-selective β -Blockers (as *proranolol*) Alone as they cause more hypertension due to unopposed α -effect.

N.B. α -blockers may be also used pre-operative and intra-operative to avoid elevation of B.P during excision of pheochromocytoma.

Drugs used in diagnosis of pheochromocytoma:

1. α -Blockers as *phentolamine* (Regitine test) Marked in B.P in sustained pheochromocytoma.
2. *Clonidine* (Clonidine suppression test) can't release of catecholamines in sustained pheochromocytoma.
3. *Methacholine* and *Histamine* release of catecholamines of B.P (instead of hypertension in other patients).
This is a "Provocative test" which is obsolete.

Drugs contraindicated in pheochromocytoma :

1. *Guanethidine* (inhibit uptake 1 of noradrenaline on post-synaptic α_1 -receptors on B.Vs sustained action of more in B.P)
2. Non-selective β -Blockers if used alone (see before)
3. α_1 -Agonists

14-Drugs and body characters:

A-Drugs causing alopecia:

1. Anticancer drugs.
2. Heparin (anticoagulant).
3. Colchicine (treatment and prophylaxis of acute gouty arthritis).
4. Sodium Valproate (broad spectrum antiepileptic).
5. Oxazolidinediones (antiepileptics in petit-mal epilepsy).
6. Interferons (in treatment of Hepatitis C virus "HCV").

B-Drugs used in treatment of alopecia:

1. Minoxidil sulphate
2. Pilocarpine

C-Drugs causing hirsutism:

1. Androgens.
2. Progesterone (in contraceptive pills).
3. Phenytoin (antiepileptic).

N.B: Minoxidil causes "Hypertrichosis".

D-Drugs causing Gynecomastia :

- 1 *Digitalis* (due to steroid structure)
- 2 *Spirolactone* (due to steroid structure)
- 3 *Reserpine*
Due to decrease dopamine in CNS increase prolactin
- 4 *α -methyl dopa*
- 5 *Ketoconazole* (antifungal , decrease synthesis of androgens)
- 6 *Cimetidine* (H_2 -blocker , used in treatment of peptic ulcer , causes anti-androgenic action)
- 7 *Estrogen* (given to males for treatment of cancer prostate)

15-Drug groups:

- 1 -zoline group:
 - 2 *Naphazoline*
 - 3 *Tetrahydrozoline* α_1 -Agonists , used locally as nasal decongestants
 - 4 *Xylometazoline*
 - 5 *Tolazoline* α -blocker , causes nasal congestion
- ⌚ -lol group:
 - 6 β -Blockers (*Propranolol*-*Nadolol*-*Atenolol*-*Esmolol*-.....)
(Butoxamine is selective β_2 -Blocker)
- -zosin group = selective α_1 -blockers
 - 2 *Prazosin*
 - 3 *Terazosin*
 - 4 *Doxazosin*
(Tamsulosin = selective α_{1A} -blocker used in prostatic hyperplasia)
- -nidine group = α_2 -Agonists
 - 1 *Clonidine* (anti hypertensive)
 - 2 *Apraclonidine*
Used in glaucoma
 - 3 *Brimonidine*
 - 4 *Tizanidine* (central skeletal muscle relaxant)

- -zepine group = selective M₁-blocker (useful in treatment of peptic ulcer)

5 Pireuzepine

6 Telenzepine

- -stigmine = carbamates , reversible anticholine-esterases :

7 Physostigmine

8 Rivastigmine (in Alzheimer)

9 Neostigmine

In myasthenia gravis

4 Pyridostigmine

- 5 -triptan group : used in acute migraine headache , agonists on 5HT_{1D}

6 Sumatriptan

7 Rizotriptan

8 Zolmitriptan

9 Ranitriptan

- -tropium group = Atropine substitutes in bronchia asthma

10 Ipratropium

11 Oxytropium

12 Tiotropium

- * -tropine group = Atropine substitutes

1 Benzotropine (in Parkinsonism)

2 Homatropine

Mydriatics

3 Eucatropine

- -curium and curonium group = Competitive neuro-muscular blockers

4 Atracurium

5 Cis-atracurium

6 Mivacurium

7 Pancuronium

8 Vecuronium

9 Alcuronium

- 10 -tidine group = H₂-Blockers used in peptic ulcer

11 Cimetidine (+ HME inhibitor + Gynecomastia and infertility)

12 Famotidine

13 Ranitidine

14 Nizatidine

- -setron group = 5HT₃-Antagonists used as anti-emetics in cancer chemotherapy and radiotherapy

15 Ondansetron

- 16 *Granisetron*
- 17 *Tropisetron*
- -*lukast* group = Leukotriene receptor antagonist used in prophylaxis of bronchial asthma
 - 18 *Montelukast*
 - 19 *Zafirlukast*
- -*zolamide* group = Carbonic Anhydrase Inhibitors
 - 20 *Acetazolamide*
 - 21 *Methazolamide* See diuretics
 - 22 *Ethoxzolamide*
 - 23 *Dorzolamide* (eye drops in glaucoma)
- -*dipine* group = Dihydropyridine calcium channel blockers (cause arteriodilatation more than cardiac dep.)
 - 24 *Nifedipine*
 - 25 *Amlodipine*
 - 26 *Nimodipine*
 - 27 *Felodipine*
 - 28 *Nicardipine*
 - 29 *Isradipine*
- -*pril* group = ACE Inhibitors
 - 30 *Captopril*
 - 31 *Lisinopril*
 - 32 *Enalapril*
- -*sartan* group = ARBs (Angiotensin-Receptor Blockers)
 - 1 *Losartan*
 - 2 *Valsartan*
 - 3 *Candesartan*
 - 4 *Telmisartan*
- -*caine* group = Na⁺ channel blockers acting as local anaesthetics
 - 5 *Procaine*
 - 6 *Tetracaine*
 - 7 *Lidocaine* (which is also antiarrhythmic)

Take care :

- Butyryl choline esterase = Pseudocholine esterase
- Scopolamine = Hyoscine
- Suxamethonium = Succinyl choline

- Isoproterenol = Isoprenaline
- Epinephrine = Adrenaline
- Norepinephrine = Noradrenaline

G-protein coupled receptors

G_s Stimulation of adenyl cyclase (A.C.) enzyme increase cAMP
 1- All β -receptors (β_1 , β_2 , β_3)
 2- H_2 -receptors (in heart , parietal cells of stomach, B.Vs)

G_q Stimulation of phospholipase C (PLC) increase Diacyl glycerol
 (DAG) and inositol triphosphate (IP_3) increase Ca^{2+} spasmogenic
 Except in endothelium of B.Vs release of nitric oxide increase
 cGMP V.D.
 1 α_1 -receptors
 2 M_1 -receptors
 3 M_3 -receptors
 4 H_1 -receptors (in smooth muscle fibres as bronchi-B.Vs-skin)
 5 $5HT_2$ -receptors (in CNS-smooth muscle fibres as bronchi-platelets)
 6 AT_1 -receptors (AT II acts on AT_1 -receptors V.C , increase aldosterone
 , increase sympathetic activity and trophic changes in heart and B.Vs)

G_i Inhibit adenyl cyclase decrease cAMP
 1 α_2 receptors (presynaptic-CNS-inhibit renin secretion)
 2 M_2 -receptors (Heart-presynaptic)
 3 $5HT_1$ -receptors (in CNS)
 4 H_3 -receptors (presynaptic-CNS)

*** Therapeutic uses of Ergot Alkaloids :**

1. Acute attack of Migraine headache :
 Ergotamine , Dihydroergotamine , cafergot
2. Prophylaxis of migraine headache : *Methysergide* (anti-serotonin)
3. Prevention & treatment of post-partum hemorrhage
4. Involution of the uterus after delivery *Ergomrtrine &*
5. Diagnosis of Prinzmetal angina *Methylergometrine*
6. Senile cerebrovascular insufficiency: *Dihydroergotoxine*
7. PVD : *Dihydroergotoxine*

8. Parkinsonism

Bromocriptine

9. Hyperprolactinemia in males and females

(D₂-agonist that crosses BBB)